Angina In Patients with Non-Obstructive Coronary Angiograms: Six-Years Follow-up

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Introduction
Flow-limiting atherosclerotic lesions in the epicardial coronary arteries have long been recognized as the underlying pathological mechanism for myocardial ischemia in patients with angina [1,2]. However, approximately one third of patients undergoing coronary angiography for angina have no significant coronary artery stenosis [3]. In these patients a number of mechanisms for chest pain have been proposed including microvascular disease, diffuse arterial wall calcification and non-cardiac causes [4–8], but little is known about related cardiovascular (CV) events. Conventional management of these patients used to be only reassurance based on the perceived good prognosis [9–11]. Such approach resulted in frequent clinical visits, repeated investigations without satisfactory explanation of symptoms, development of depression and a shift towards alternative medical assistance [12–14]. Recent studies have shown such patients to have increased risk of major CV events compared with asymptomatic reference population [15–18]. This study aims at evaluating the long term persistence of angina and occurrence of major CV events in a cohort of patients with stable angina and non-obstructive coronary angiograms.

Methods
We retrospectively evaluated all patients presented between 1st July 2008 and 31st December 2009, who received elective cardiac assessment and coronary angiography at the Cardiovascular Unit.

Highlights
Background
About one third of patients undergoing coronary angiography for angina have non-obstructive coronary artery disease (CAD). Until recent years the prognosis has been thought to be favourable and no treatment were recommended. More recently, an increased risk of cardiovascular (CV) events has been documented in these patients compared with a general population. We aimed to evaluate the long term persistence of angina and the occurrence of major CV events in patients with stable angina and non-obstructive CAD.

Methods
We retrospectively evaluated all patients with effort angina referred to the cardiac catheterization laboratory of the Cardiovascular Unit, University of Catania, Sicily, between 1st July 2008 and 31st December 2009, because of a clinical suspicion of myocardial ischemia, without obstructive CAD, defined as <50% stenosis of left main stem or <70% in any epicardial coronary artery.

Results
Among 2574 patients (2025 men and 549 women) referred for diagnostic coronary angiography, 151 (5.8%) had non-obstructive coronary angiograms. Six-years follow-up was available in 127 patients (63 men and 64 women). Persistence of angina was reported in 20.4%. Four patients (3.1%) had acute myocardial infarction and two (1.6%) had stroke.

Conclusions
During a six-years follow-up, persistence of angina and occurrence of acute major CV events were found in a significant proportion of patients with stable angina and non-obstructive coronary angiograms.

Keywords: Coronary Artery Disease; Angina Pectoris; Coronary Angiography

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of the University of Catania, Sicily, because of clinical suspicion of obstructive coronary artery disease as a cause for chest pain. All patients had a positive stress test defined as >1 mm ST shift in more than one lead or already existing ECG changes at rest (ST depression or T wave inversion). Typical angina was defined as exertional chest pain relieved by rest or nitrates. All patients received a diagnostic coronary angiogram through the femoral artery, using conventional Judkins procedure. Non-obstructive coronary disease was defined as <50% stenosis of the left main stem artery or <70% in any of the epicardial coronary arteries [19]. Patients were excluded if they had recent or previous myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft, heart failure with reduced left ventricular ejection fraction, ≤40% on echocardiography, aortic stenosis or hypertrophic cardiomyopathy.

For each patient, name, gender, age, address, telephone number and CV risk factors details were collected from the clinical records. Systemic arterial hypertension was defined as a systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or taking treatment of hypertension. Dyslipidaemia was defined as total cholesterol >240 mg/dl, HDL-cholesterol <40 mg/dl (men) or <50 mg/dl (women), LDL-cholesterol >115 mg/dl, or taking treatment for dyslipidemia. Diabetes was defined as fasting blood glucose level >126 mg/dl or use of hypoglycemic medications. Smoking was defined as current or never. Family history of coronary artery disease (CAD) was defined as the presence of first-degree family member with CAD before 60 years of age. The burden of these CV risk factors for each patient was calculated as a score, counting 1 for each risk factor. Patients with previous myocardial infarction and obstructive coronary disease were excluded from the calculation of the score.

The patients included in the study had telephone medical consultation by one of the authors (SV) in 2015, to collect information about persistence of angina and/or occurrence of CV events defined as acute myocardial infarction or stroke.

Statistical analysis
Continuous variables are expressed as mean (SD) and categorical variables as frequencies. Differences between means were tested using unpaired two-sample Student t-test and differences between frequencies using Chi-square. The mean value of the CV risk factor score for each group of patients was calculated as the sum of the scores divided by the number of patients. The relationship between CV risk factors and the persistence of symptoms at follow-up was estimated with a logistic regression, using persistence of symptoms as a response and CV risk factors as independent variables. Statistical analyses were carried out using STATA 11.

Results
At baseline:
During the study period, 2574 patients (2025 men and 549 women) were referred for diagnostic coronary angiography because of exertional angina. Non-obstructive CAD was found in 151 (5.8%). These patients formed the study group. Compared to the rest of the population found to have significant coronary stenosis, the patients with non-obstructive disease were younger and a greater proportion were women. Also, the prevalence of diabetes and smoking was significantly less frequent in the non-obstructive group compared to those with significant coronary stenosis (Table 1). Hypertension and dyslipidaemia were almost equally present in about half of the two groups of patients. Only few patients did not have any of the conventional CV risk factors, however their proportion was almost double in the non-obstructive group, although the difference was not statistically significant.

Of the non-obstructive coronary disease, 79 were men (52.3%) and 72 women (47.7%) and the proportion of women was significantly higher than in the coronary obstructive group (Table 1). Women in the non-obstructive coronary disease group were older (63.3 (9.6) vs. 59.5 (12.1) years, p=0.03) and had higher prevalence of dyslipidaemia than men. In the same group, more men smoked than women. The prevalence of hypertension, diabetes and family history of CAD was not different between genders (Table 2).

The mean value of the CV risk factors score was significantly greater in the obstructive coronary stenosis group compared to the non-obstructive group [2.6 (1.0) vs. 2.3 (1.0), p=0.04].

At follow-up:
Follow-up data were available in 127/151 patients (63 men and 64 women) with non-obstructive CAD. The remaining 24 patients could not be contacted for several reasons, including change of address, wrong telephone number or they refused to give information. In this subgroup of patients, there was no age difference between women and men (63.7 (9.1) vs. 60.4 (12.6) years, p=0.09). Persistence of exertional chest pain was reported in one fifth of patients, again with no gender difference (Table 3). Overall, an acute CV event occurred in 4.7% at follow-up, 2 - 5 years after the initial angiogram. Four patients (3.1%) had acute myocardial infarction (one of whom died) and two (1.6%) had stroke. Persistence of symptoms did not correlate with the class of antiangiinal drugs that patients were taking or with withdrawal of treatment. Patients with persistent angina had lower mean value of CV risk scores than those without angina (1.9 (1.0) vs. 2.4 (1.1), p=0.04). No difference was found between the CV risk score of these patients and those who had cardiovascular events (2.1 (0.4), p=0.6). Dyslipidaemia was less frequent in patients with

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of baseline demographic characteristics and CV risk factors between patients with obstructive and non-obstructive coronary artery stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>non-obstructive</td>
</tr>
<tr>
<td>n=151</td>
<td>n=2423</td>
</tr>
<tr>
<td>Age y (SD)</td>
<td>61.3 (11.1)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>72 (47.7)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>93 (61.6)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>30 (19.8)</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>66 (43.7)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>34 (22.5)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>51 (33.7)</td>
</tr>
<tr>
<td>No risk factor</td>
<td>5 (3.3)</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD) or proportions. Comparisons are made using independent t-test or Chi2 test. Each patient may present one or more risk factors.
consistent with previous reports [21].

women was as twice as in those with significant stenosis, thus low percentage of such patients in our cohort, the prevalence of diagnosis of the coronary status than others [20]. Despite the differences in the strategic management of patients between from 2% to 62% [3,9,11,14,16]. Such large variability reflects undergoing elective diagnostic coronary angiography, ranging an anatomically non-obstructive coronary disease in patients Previous studies have reported large variability in the rate of CV risk factors in the non-obstructive coronary artery stenosis group (n= 151)

<table>
<thead>
<tr>
<th></th>
<th>men (n= 79)</th>
<th>women (n= 72)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>45 (56.9)</td>
<td>48 (66.7)</td>
<td>0.21</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (16.4)</td>
<td>17 (23.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>27 (34.1)</td>
<td>39 (54.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>27 (34.1)</td>
<td>7 (9.7)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>22 (27.8)</td>
<td>29 (40.2)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Each patient may present one or more risk factors

persistent angina at follow-up than in patients without angina. The other CV risk factors did not show any significant difference (Tables 4). Diabetes increased three times the risk of persistent angina at follow-up (Table 5).

Discussion

Findings

Our results show that about 6% of patients with stable angina have non-obstructive coronary disease on conventional routine angiography. These patients were younger and had a lower prevalence of diabetes, smoking and an overall lower risk factors score than those with obstructive disease. After six-years follow-up, one in five of the patients with non-obstructive coronary disease continued to experience angina and one in twenty had an acute CV event. Compared to patients who remained asymptomatic after six-years follow-up, those who experienced angina had lower cholesterol and overall CV risk factor burden. Finally, those who developed acute CV events (4.7%) did not have any specific risk factors pattern or relationship between risk factors and events.

Data interpretation

Previous studies have reported large variability in the rate of anatomically non-obstructive coronary disease in patients undergoing elective diagnostic coronary angiography, ranging from 2% to 62% [3,9,11,14,16]. Such large variability reflects differences in the strategic management of patients between centres with some more proactive in offering direct anatomical diagnosis of the coronary status than others [20]. Despite the low percentage of such patients in our cohort, the prevalence of women was as twice as in those with significant stenosis, thus consistent with previous reports [21].

Another variability is the percentage of patients who continued to complain of angina at follow-up. While 20% of our patients fell in this category, a significant higher percentage has been reported by others, even at shorter follow-up [14,22]. This raises the question about the nature of the angina like chest pain that patients complain of, which could be explained by either calcified epicardial vessels or microcirculation disease [4,23-26] or else non-cardiac in origin, e.g. gastroesophageal reflux, psychiatric disorders or musculoskeletal [27].

Aside from the angina symptoms, the overall acute CV event rate during the 6 year follow-up was low, which support the current perception that patients with non-obstructive coronary disease have good prognosis [22,28]. But the prevalence of acute events in our group seem to be higher than the respective rates in the general population in Italy, being 2.2% for myocardial infarction and 1.4% for stroke [29].

Such comparisons cannot be fully justified, since our patients were symptomatic and many were found to have coronary disease, even in the absence of significant stenoses. Furthermore, our patients with acute events did not show any relationship between events and conventional risk factors of atherosclerosis and they developed the events while on full risk controlling medications. Likewise, patients with consistent angina at follow-up were not different in the extent of risk factors they carried, except for a lower rate of dyslipidaemia, when compared to the asymptomatic patients. This finding to some extent contradicts the relevant use of risk factors for predicting symptoms or events, well established in the Framingham Study [30].

Finally, compared to our patients with non-obstructive coronary disease, those with significant stenosis had higher rates of diabetes and smoking and overall CV risk burden, thus confirming the potential relevance of risk factors in the development of obstructive coronary disease. This however, remains to be retested in a larger sample of patients.

Limitations

This study has several potential limitations. First, it is a relatively small-, single-centre study. Therefore our results may not be applicable to other patients in different geographical areas.

Table 4 CV risk factors according to the persistence of angina at follow-up (n=127)

<table>
<thead>
<tr>
<th></th>
<th>no angina (n=101)</th>
<th>angina (n= 26)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>62.6 (10.6)</td>
<td>60.0 (12.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Men</td>
<td>50.5</td>
<td>46.1</td>
<td>0.69</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80.2</td>
<td>69.2</td>
<td>0.23</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28.7</td>
<td>34.6</td>
<td>0.55</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>58.4</td>
<td>26.9</td>
<td>0.004</td>
</tr>
<tr>
<td>Smoking</td>
<td>28.7</td>
<td>26.9</td>
<td>0.85</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>44.5</td>
<td>30.7</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD) or proportions. Comparisons are made using independent t-test or chi2 test. Each patient may present one or more risk factors.
Second, because the study was retrospective and dependent upon the hospital clinical records, there is the possibility of some inaccuracies of the information coded into the database. Third, the persistence of angina at follow-up was dependent upon the subjective judgment of patients. Therefore, the non-cardiac origin of the chest pain in some patients cannot be excluded. Fourth, we did not perform coronary angiograms at follow-up. Hence, it is possible that some patients might have had a progression of coronary lesions without symptoms as has previously been shown [31]. Sixth, occult coronary abnormalities and microvascular dysfunction leading to abnormal myocardial perfusion were not investigated.

**Clinical implications**

Although the population sample we studied was relatively small, our observations suggest that patients with angina, even in the absence of obstructive coronary stenosis, cannot be considered at low CV risk and need to be fully investigated for better assessment of angina and atherosclerosis risk factors control, since a minority might continue to develop symptoms or acute events.

**Conclusions**

A significant proportion of patients with stable angina and non-obstructive coronary stenosis continue complaining of persistent chest pain after six years after the initial coronary angiogram, and carry risk for acute events higher than the general population. CV risk factors burden in these patients was lower than in those with obstructive coronary stenosis. Furthermore, persisting angina and acute major CV events were not related to a greater CV risk factors burden. This seems to indicate that in patients with insignificant coronary stenosis the degree and the extension of coronary obstruction is unrelated to the persistence of symptoms and to the occurrence of CV events.

**Declarations of Interest**

The authors declare no conflicts of interest.

**Acknowledgements**

The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals” [32].

### Table 5 Relationship between CV risk factors and persistence of symptoms at follow-up

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>3.29</td>
<td>0.01</td>
<td>1.22-8.81</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.82</td>
<td>0.18</td>
<td>0.74-4.43</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>1.48</td>
<td>0.52</td>
<td>0.43-5.11</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>1.21</td>
<td>0.86</td>
<td>0.12-11.4</td>
</tr>
<tr>
<td>Sex</td>
<td>1.19</td>
<td>0.68</td>
<td>0.50-2.82</td>
</tr>
<tr>
<td>Age</td>
<td>0.97</td>
<td>0.27</td>
<td>0.94-1.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.96</td>
<td>0.95</td>
<td>0.29-3.18</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.83</td>
<td>0.77</td>
<td>0.25-2.73</td>
</tr>
</tbody>
</table>

### References


